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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/696,391

10/28/2003

Jeffrey Isner

47624-CIP (71417)

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21874 7590 02/13/2007

EDWARDS & ANGELL, LLP

P.O. BOX 55874

BOSTON, MA 02205

EXAMINER

NGUYEN, QUANG

ART UNIT

PAPER NUMBER

1633

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

02/13/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/696,391

Applicant(s)

ISNER ET AL.

Examiner

Quang Nguyen, Ph.D.

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 December 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 49-52, 54-65 and 68 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 49-52, 54-65 and 68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/26/06 has been entered.

Amended claims 49-52, 54-65 and 68 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claims 58-59 are objected to because of the phrase "EPC bone marrow derived EPC". The term "EPC" is recited twice in the same phrase. Appropriate correction is required.

Priority

The present application is a continuation-in-part of U.S. Serial No. 09/265,071, filed on 3/9/1999, now issued US 6,676,937, which claims benefit of the provisional application 60/077,262, filed on 3/9/1998.

Upon review of the specifications of the U.S. Serial No. 09/265,071 and the provisional application 60/077,262 and comparison with the specification of the present application, it is determined that the examined claims are only entitled to the priority

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benefit of the filing date of 10/28/2003 for the following reasons. This is because there is no written support in either the parent U.S. application or in the provisional application for a method of inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment having the specific recited steps (a)-(c), and particularly comprising **the step of monitoring a cardiac function as recited in step (c); or the step of administering to the treated mammal a broad genus of an anti-coagulant before, during, or after administration of the nucleic acid to the mammal** (limitation of claim 61).

Accordingly, pending claims 49-52, 54-65 and 68 are only entitled to the priority date of 10/28/2003 for the reasons set forth above.

Should Applicants overcome the assigned priority date of 10/28/2003, claims 49-52, 54-65 and 68 are only entitled **at best to the effective filing date of 3/9/1999** because the provisional application 60/077,262, filed on 3/9/1998 does not have a written support for a concept of co-administering a broad genus of an angiogenic factor or an effective fragment thereof to induce new blood vessel growth in the myocardial tissue of the mammal and increasing the frequency of EPC in the mammal, particularly VEGF, SCF and any CSF, with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Amended claims 49, 52, 54-56, 58-65 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307; Cited previously) in view of Hammond et al. (US Patent 5,880,090; IDS) and Dillmann et al. (US 6,605,274; Cited previously). ***This is a modified rejection.***

The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such a treatment comprising: a) administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal; and c) monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension, end-systolic dimension, fractional shortening, wall motion score index, electromechanical mapping, cardiac angiography or LV systolic pressure, wherein the method improves said cardiac function.

Isner teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and myocardial ischemia (page 4, lines 5-23). The method comprises the step of injecting to said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein by any injection means, and the nucleic acid may be carried by vehicles such as cationic liposomes, adenoviral vectors and that nucleic acid encoding different angiogenic proteins may be used separately or simultaneously (page 4, line 25 continues to line 8 of page 5). Angiogenic proteins include aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxide synthase or muteins or portions thereof (page 5, lines 10-22). Isner also teaches that the nucleic acid encoding an angiogenic protein is inserted into a cassette where it is operably linked to a promoter that is capable of driving expression of the protein in cells of the desired target tissue (page 9, line 28 continues to line 20 of page 10). Isner further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxide synthase, L-arginine, fibronectin, urokinase, plasminogen activator and heparin (page 11, lines 15-19). Isner also discloses that catheters have been used for gene delivered in the art (page 1, line 23 continues to line 30 of page 2).

Isner does not teach specifically a further administration of an effective amount of at least one angiogenic factor, specifically a stem cell factor (SCF), a colony stimulating factor (CSF), or an effective fragment thereof into the mammal to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells, even though Isner teaches that nucleic acids encoding different angiogenic proteins such as aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxide synthase or muteins or portions thereof may be used separately or simultaneously; and that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells. Isner also does not teach specifically to monitor a cardiac function by one of the recited approaches, even though Isner discloses monitoring collateral artery development in the medial thigh by angiography (page 21, lines 10-25) or measuring calf blood pressure for physiologic assessment (page 22, lines 12-27).

At the filing date of the present application (10/28/03) Hammond et al already taught that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al further note that CD34+ circulating cells in the blood can participate in the repair of ischemic tissue (col. 3, lines 28-37).

Dillmann et al already taught that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart failure (CHF) are well known to those of ordinary skill in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance studies (col. 14, lines 14-26), as well as measurements of left ventricular end-diastole dimension (LVEDD), LV end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by further administering specifically to the treated mammal an effective amount of at least one of SCF or CSF or an effective fragment thereof to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal in light of the teachings of Hammond et al. Additionally, it would also have been obvious for an ordinary skilled artisan to monitor the cardiac function in the mammal treated for myocardial ischemia using any of the means recited in claim 49 in light of the teachings of Dillmann et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient; and this mobilization of endothelial cell

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progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome. Additionally, any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance. It is further noted that the monitoring means is not the patentable subject matter for the claimed methods because Applicants specifically state "cardiac function is monitored in the mammal by one or more combination of standard approaches to evaluate therapeutic outcome" (page 12, lines 24-25). The modified method resulting from the combined teachings of Isner, Hammond et al., and Dillman et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner, Hammond et al., and Dillman et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Amended claims 50-51 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307; Cited previously) in view of Hammond et al. (US Patent 5,880,090; IDS) and Dillmann et al. (US 6,605,274; Cited previously) as

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applied to claims 49, 52, 54-56, 58-65 and 68 above, and further in view of Asahara et al. (EMBO Journal 18:3964-3972, 1999). ***This is a new ground of rejection.***

The combined teachings of Isner, Hammond et al. and Dillmann et al. were presented above. However, none of the references teaches specifically a further administration to the mammal an effective amount of a VEGF or an effective fragment thereof to induce the new blood vessel growth in the myocardial tissue of the mammal and increasing the frequency of endothelial progenitor cells in the mammal.

However at the filing date of the present application (10/28/2003), Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated endothelial cells (see at least the abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method of Isner, Hammond et al and Dillman et al. by also further administering to the treated mammal an effective amount of at least VEGF or an effective fragment thereof such as VEGF165 to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal in light of the teachings of Asahara et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated

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endothelial cells; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome. The modified method resulting from the combined teachings of Isner, Hammond et al., Dillman et al., and Asahara et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner, Hammond et al., Dillman et al., and Asahara et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejections in the Amendment filed on 12/26/06 (pages 10-16) have been fully considered but they are respectfully not found persuasive.

The examiner notes that Applicants presented a lot of similar arguments as those already presented in the Amendment after final dated 7/24/06 (pages 6-10), and these arguments have been addressed by the Examiner in the Advisor action mailed on 8/7/06. Only new arguments will be addressed below.

1. With respect to the issue of teaching away by the Hammond et al reference due to the undesirable effects, Applicants further argue that Hammond merely

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states that two dogs that received synthetic grafts had 80% and 35% of their grafts surfaces covered with endothelial cells (example 3), and that this fails to indicate whether or not the grafts were evaluated for the presence of microcalcification. Additionally, example 4 also fails to provide any description of results. Applicants further argue that the statement “**proposed** that these circulating CD34+ or Flk-1+ cells participate in the repair of ischemic tissue” is based on an *in vitro* study is insufficient to provide the requisite expectation of success or motivation to combine.

Since examples 3-4 did not mention anything about the presence of microcalcification, this means that microcalcification is not a problem. Nevertheless, the examples clearly demonstrated that exemplified G-CSF and other agents (such as SCF, GM-CSF, see allowed claims) are capable of mobilizing bone marrow derived endothelial progenitors to promote the healing of vascular grafts *in vivo*. The circulating CD34+ or Flk-1+ cells can participate in the repair of ischemic tissue as proposed by Asahara et al. is not based only on *in vitro* study as alleged by Applicants as evidenced at least by the results demonstrated by Asahara et al (Science 275:965-967, 1997; Cited by Hammond et al.) showing that the EC progenitors can be incorporated into sites of active angiogenesis in animal models of ischemia.

Once again, Isner teaches clearly that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells in a method for enhancing blood vessel formation or an angiogenesis in an ischemic tissue, including ischemic cardiomyopathy or myocardial ischemia, in a mammal. Hammond et al. teaches clearly that SCF, GM-CSF, G-CSF are capable of

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mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for enhancing the endothelialization of synthetic vascular grafts in a patient. Hammond also notes that CD34+ circulating cells in blood can participate in the repair of ischemic tissue (col. 3, lines 28-37). As already pointed out in the above rejection, an ordinary skilled artisan would have been motivated to modify the method of Isner by further administering to the treated mammal with an effective amount of at least one of SCF, GM-CSF and G-CSF, or an effective fragment thereof because Hammond already demonstrated that the aforementioned cytokines are capable of mobilizing bone-marrow derived endothelial cell progenitors in the blood, and that this mobilization of endothelial cell progenitors would further enhance blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the angiogenic therapeutic outcome. Additionally, any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance.

2. With respect to the issue of unexpected result, Applicants pointed the Examiner to page 7, line 27 of the specification that indicates that the combination of administering an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof and an effective amount of at least one angiogenic factor or an effective fragment thereof is likely to produce a synergistic

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effect. As evidence that the combination is surprisingly effective, Applicants refer the examiner to pages 54-58 showing that the combo therapy resulted in superior improvement in all indexes of perfusion and function compared with all other treatment groups. Applicants argue that none of the prior art references teaches that VEGF when administered with a cytokine would have a synergistic effect on cardiac function in ischemic myocardial tissues and that evidence of synergism is indicative of non-obviousness.

It is noted that the combo therapy resulted in superior improvement compared with other treatment groups that include a control group, a group treated only with VEGF-2 transfer and a group treated only with a cytokine (see pages 54-58 and Figures 9 and 11). There is no surprising or synergistic results obtained by the combo group as argued by Applicants (please see at least the results presented in Figure 9B; and results for LVEDD, LVESD, FS, LVEDP in Figure 11C) because the obtained results are actually expected because the angiogenic effects contributed by the administration of an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof are complemented or enhanced by the effects contributed by the administration of an effective amount of at least one angiogenic factor such as GM-CSF, G-CSF, SCF and VEGF or an effective fragment thereof due to their ability to mobilize bone-marrow derived endothelial progenitors that can participate in the repair of ischemic tissues based on the teachings of Hammond et al. and/or Asahara et al. as discussed above. Moreover, please also note that GM-CSF, G-CSF

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and VEGF are also angiogenic proteins in addition to their ability to mobilize bone-marrow derived endothelial progenitor cells.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Amended claims 49, 52, 54-56, 58-65 and 68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 49-61, 63-66 and 68-72 of copending Application No. 10/714,574 in view of Dillmann et al. (US 6,605,274; Cited previously).

The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such a treatment comprising: a) administering an effective amount of a solution comprising a nucleic acid encoding at

least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal; and c) monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension, end-systolic dimension, fractional shortening, wall motion score index, electromechanical mapping with a NOGA system, cardiac angiography or LV systolic pressure, wherein the method improves said cardiac function.

Claims 49-61, 63-66 and 68-72 of copending Application No. 10/714,574 are drawn to a method for treating ischemic myocardial tissue of a mammal in need of such a treatment comprising: a) identifying a mammal which has, is suspected of having, or will have the ischemic tissue; b) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and c) administering to the mammal an effective amount of a colony stimulating factor, including GM-CSF, or an effective fragment thereof, or an effective amount of a cytokine (e.g., GM-CSF and SCF) thereby treating ischemic myocardial tissue of the mammal.

The claims of the present application differ from the claims of the copending Application No. 10/714,574 in reciting the additional step of monitoring a cardiac function by any one of the approaches recited in the Markush group of claim 49.

At the filing date of the present application, Dillmann et al already taught that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart failure (CHF) are well known to those of ordinary skill in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance studies (col. 14, lines 14-26), as well as measurements of left ventricular end-diastole dimension (LVEDD), LV end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the method of the copending Application No. 10/714,574 by further monitor the cardiac function in the mammal treated for myocardial ischemia using any of the means recited in claim 67 in light of the teachings of Dillmann et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of the copending Application No. 10/714,574 and Dillmann et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Amended claims 49-51 and 57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 69 of copending Application No. 10/714,574 in view of Dillmann et al. (US 6,605,274; Cited previously) and Asahara et al. (EMBO Journal 18:3964-3972, 1999).

The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such a treatment comprising: a) administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal; and c) monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension, end-systolic dimension, fractional shortening, wall motion score index, electromechanical mapping with a NOGA system, cardiac angiography or LV systolic pressure, wherein the method improves said cardiac function, and wherein the angiogenic factor is a VEGF or an effective fragment thereof.

Claim 69 of copending Application No. 10/714,574 is drawn to a method for treating ischemic myocardial tissue of a mammal in need of such a treatment comprising: a) administering to a mammal an effective amount of a cytokine that mobilizes endothelial progenitor cells; and b) subsequently administering an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue, wherein the method increases the neovascularization of said tissue thereby treating ischemic myocardial tissue of the mammal.

The claims of the present application differ from the claims of the copending Application No. 10/714,574 in reciting the additional step of monitoring a cardiac function by any one of the approaches recited in the Markush group of claim 49, and the angiogenic factor is VEGF or an effective fragment thereof.

At the filing date of the present application, Asahara et al already demonstrated that recombinant human VEGF₁₆₅ is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated endothelial cells (see at least the abstract).

Additionally, Dillmann et al already taught that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart failure (CHF) are well known to those of ordinary skill in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance studies (col. 14, lines 14-26), as well as measurements of left

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ventricular end-diastole dimension (LVEDD), LV end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the method of the copending Application No. 10/714,574 by further monitor the cardiac function in the mammal treated for myocardial ischemia using any of the means recited in claim 67 in light of the teachings of Dillmann et al., as well as further administering to the treated mammal an effective amount of at least VEGF or an effective fragment thereof such as VEGF165 to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal in light of the teachings of Asahara et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance. Furthermore, Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated endothelial cells; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome.

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An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of the copending Application No. 10/714,574, Dillmann et al., and Asahara et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection.

Conclusions

No claims are allowed.

Should Applicants desire a telephonic interview, please contact the undersigned examiner by telephone to schedule an interview.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Truong
QUANG NGUYEN, PhD
PATENT EXAMINER